REMARKS

The Office Action mailed June 6, 2003 has been received and reviewed. Claims 2, 21, 25, 28-32, 37, 44, 48-51, 54-65, and 69-71 are pending in the application. All claims stand rejected. Claims 2, 21, 25, 37, 44, 50, 51, 56, 58, 60, 61 and 69 have been amended and claims 19, 38-40, 42, 45-49, 52-53, 55, 63 and 66-68 have been canceled as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Applicants would like the Examiner for the courtesy extended in the interview of August 6, 2003. It was very helpful in understanding the rejections.

Specification

The specification was objected to as lacking Sequence Identifiers corresponding to sequences in the specification. Applicants have added sequence identifiers to the Brief Description of the Drawings where appropriate as is permitted in the M.P.E.P. (*See*, M.P.E.P. § 2429, page 2400-55). Withdrawal of the objection is thus requested.

Claims Rejections Under 35 U.S.C. § 112, second paragraph

Claims 51-54, 56 and 57

Claims 51-54, 56 and 57 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 52 and 53 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

Specifically, it was thought that claims 51-54, 56 and 57 were vague for use of the phrase "adenoviral nucleic acid incorporated within said recombinant virus capsid." (Office Action, mailed June 6, 2003, p. 3).

As discussed at the interview, claims 51 and 56 have been amended such that the adenoviral nucleic acid or the non-adenoviral nucleic acid is incorporated within a genome of the recombinant adenovirus, respectively. Thus, claims 51, 54, 56 and 57 should be definite and

reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejections of claims 51, 54, 56 and 57 are requested.

Claims 2, 21, 25, 38-40, 42, 60-65 and 69-70

Claims 2, 21, 25, 38-40, 42, 60-65, and 69-70 stand rejected under 35 U.S.C. § 112, second paragraph, for assertedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 38-40, 42 and 63 have been canceled rendering the rejections thereof moot. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, the phrase "with reduced tissue tropism for liver cells" in claims 2 and 25 was thought to be vague and indefinite. Although applicants do not agree that the claims lack compliance with 35 U.S.C. § 112, second paragraph, as discussed at the interview, claims 2, 25, 60 and 69 have been amended to include a comparison to the corresponding *wild type* adenovirus as suggested by the Examiner.

Accordingly, reconsideration and withdrawal of the indefiniteness rejections of claims 2, 21, 25, 60-62, 64 and 69-70 are requested.

Claim 37

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, for assertedly being incomplete for omitting essential steps, "such omission amounting to a gap between the steps." (Office Action, p. 5). Applicants respectfully traverse the rejection.

Although applicants do not agree that essential steps are missing, to expedite prosecution, claim 37 has been amended as discussed at the interview to include the phrase "thus reducing the tissue tropism of the adenovirus capsid for liver cells as compared to the corresponding *wild type* adenovirus capsid." Accordingly, reconsideration and withdrawal of the rejection of claim 37 are requested.

Claims Rejections Under 35 U.S.C. § 112, first paragraph

Written Description Rejections

Claims 2, 21, 25, 38-40, 42, 44-65, and 69-71

Claims 2, 21, 25, 38-40, 42, 44-65, and 69-71 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." (Office Action, page 5.) Claims 38-40, 42, 45-49, 52-53, 55 and 63 have been canceled rendering the rejections thereof moot. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, it was thought that the claims "encompass any recombinant adenovirus having various capsid proteins or fiber proteins from **any virus**, including **any adenovirus** and **any non-adenovirus**, and said recombinant adenovirus has at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, or with a reduced tissue tropism for liver cells, and the tropism could be provided by a virus capsid comprising protein **fragments** from at least two different viruses." (*Id.* at p. 6-7) (emphasis in original). Further, it was thought that "[t]he claims (especially, claims 2, 25, 37, 44, 60, 66 and 69) read on recombinant virus having reduced tropism for liver cells, or increased tropism for endothelial cell or smooth muscle cells as compared to any other adenovirus capsid or *any virus*." (*Id.* at p. 7) (emphasis added).

Although applicants do not agree that the claims do not comply with the written description requirement, to expedite prosecution, the independent claims have been amended to include the specific adenoviral serotypes that confer a reduced tissue tropism for liver cells or an increased tissue tropism for smooth muscle cells or endothelial cells as disclosed in the specification as discussed at the interview. Since the specification discloses the structural features of the recombinant adenovirus or capsid that reduces the tissue tropism for liver cells, (*See*, Specification, p. 38, line 4 through p. 45, line 5 and Table II, page 47) claims 2, 25, 37 and 69, and the claims depending therefrom, are in compliance with the written description requirement.

Further, since the specification discloses the structural features of the recombinant adenovirus or capsid having an increased tissue tropism for smooth muscle cells or endothelial cells, (*See, Id.* at page 42, lines 9-30 and FIG. 8D) claims 44, 58 and 60, and the claims depending therefrom, comply with the written description requirement.

Accordingly, reconsideration and withdrawal of the written description rejection of claims 2, 21, 25, 44, 50-51, 54-55, 56-62. 64 and 69-71 are requested.

Claims 28-32

Claims 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for assertedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, p. 17). Applicants respectfully traverse the rejections as hereinafter set forth.

Specifically, it was thought that "[c]laims 28-32 recite adenovirus sequences without providing adequate sequence information regarding the genome of the adenovirus claimed. This rejection may be obviated by appropriate deposit of the nucleic acid construct claimed. The declaration by Dr. Jaap Goudsmit only indicates deposit of ECACC 96022940 . . ." (*Id.*) Attached herewith for the Examiner's convenience are copies of the "Declaration Under 37 C.F.R. §§ 1.801-1.809" signed by Dr. Ton Logtenberg on February 28, 2002, as well as confirmation certification documents for each ECACC submission received from ECACC encompassing ECACC deposit references 01121708, 01121710, 01121709, 01121711 and 0112712. These documents were previously submitted to the Office on February 28, 2002.

Accordingly, reconsideration and withdrawal of the rejection of claims 28-32 are requested.

Enablement Rejections

Claims 2, 19, 21, 25, 28-32, 37-40, 42 and 44-71

Claims 2, 19, 21, 25, 28-32, 37-40, 42, and 44-71 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement. Claims 19, 38-40, 42, 45-49, 52-53, 55, 63 and

66-68 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

Specifically, it was thought that the claims are not enabled for "any recombinant adenovirus with a reduced tropism for liver cells, any adenovirus capsid with a reduced tissue tropism for liver cells . . . , any recombinant adenovirus comprising a recombinant virus capsid having protein fragments from at least two different viruses . . . , a pharmaceutical composition comprising the recombinant adenovirus of claim 2, cells for producing a recombinant adenovirus having tissue tropism for smooth muscle cells . . . , and any recombinant adenovirus having a capsid with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells, ..." (Office Action, p. 9-10).

Although applicants do not agree that the claims are not enabled, as discussed at the interview, the independent claims have been amended to include the serotypes corresponding with the reduced tropism for liver cells or the increased tissue tropism for endothelial cells or smooth muscle cells. For instance, amended claims 2, 25 and 37 are directed to a recombinant adenovirus or capsid having a reduced tissue tropism for liver cells, wherein a portion of the fiber protein is of a serotype of adenovirus 12, 16, 28 or 40-L, and claim 69 is directed to a recombinant adenovirus capsid having a chimer fiber protein having the knob domain of adenovirus serotype 16. Since the specification discloses recombinant adenovirus having a reduced tissue tropism for liver cells that corresponds to the elements of claims 2, 25 37 and 69 (*See*, Specification at p. 38, line 4 through p. 45, line 5 and Table II, page 47), claims 2, 25, 37 and 69, and the claims depending therefrom are enabled.

Independent claims 44, 58 and 60 have been amended to read on the adenovirus subtypes 11, 16, 35 and 51. Since the specification discloses recombinant adenovirus or capsids having an increased tissue tropism for endothelial cells or smooth muscle cells, (*See*, *Id.* at page 42, lines 9-30 and FIG. 8D) claims 44, 58 and 60, and the claims depending therefrom, are enabled.

With regard to independent claim 37, it is directed to a method for reducing a tissue tropism of an adenovirus capsid for liver cells, wherein a first nucleic acid encoding a tissue-tropism determining peptide of a fiber protein is exchanged for a second nucleic acid encoding a tissue-tropism determining fragment of a fiber protein an adenovirus 12, 16, 28 or 40-L. Since

the specification discloses methods of reducing a tissue tropism of a recombinant adenovirus using peptides of a fiber protein of a serotype of adenovirus 12, 16, 28 or 40-L, (*See, Id.* at p. 38, line 4 through p. 45, line 5 and Table II, page 47) claim 37 is enabled.

Accordingly, reconsideration and withdrawal of the enablement rejection of 2, 21, 25, 28-32, 37, 44, 50-51, 54, 56-62, 64, 65 and 69-71 requested.

Claim 21

Claim 21 stands rejected as assertedly lacking enablement for a pharmaceutical composition comprising the recombinant adenovirus of claim 2. In view of the amendment to claim 21, applicants respectfully traverse the rejection.

Although applicants do not agree that claim 21 is not enabled, to expedite prosecution, the term "pharmaceutical" has been removed from claim 21. Accordingly, reconsideration and withdrawal of the enablement rejection of claim 21 is requested.

Claim Rejections Under 35 U.S.C. § 102(b)

Claim 58 stands rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Stevenson *et al.*, 1997 (Journal of Virology, Vol. 71, No. 6, p. 4782-4790)." Applicants respectfully traverse the rejection as hereinafter set forth.

Stevenson *et al.* does not anticipate claim 58 since each and every element of claim 58 is not disclosed by Stevenson *et al.* As amended, claim 58 is directed to a "recombinant adenovirus having an increased tropism for endothelial cells or smooth muscle cells as compared to the corresponding *wild type* adenovirus ... wherein at least one of the peptides comprises at least a tissue tropism determining region of a fiber protein, said fiber protein being a fiber protein of an adenovirus selected from the group consisting of adenovirus 11, adenovirus 16, adenovirus 35, and adenovirus 51."

Stevenson *et al.* does not disclose a recombinant adenovirus capsid having a tissue tropism determining region of a fiber protein of adenovirus 11, adenovirus 16, adenovirus 35 or adenovirus 51. Rather, the chimeric fiber of Stevenson includes head domain of the fiber protein from Ad3. (*See*, Stevenson et al., Abstract and p. 4784).

Accordingly, reconsideration and withdrawal of the anticipation rejection of claim 58 is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the applicants respectfully submit that the claims define patentable subject matter. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Office respectfully is invited to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Date: August 27, 2003
AFN/tjs
Document in ProLaw

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Vogels et al.

Serial No.: 09/444,284

Filed: 19 November 1999

For: GENE DELIVERY VECTORS PROVIDED WITH A TISSUE TROPISM FOR SMOOTH MUSCLE CELLS, AND/OR ENDOTHELIAL CELLS

Examiner: S. Chen

Group Art Unit: 1633

Attorney Docket No.: 4231US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: _____

Date of Deposit with USPS: _____

Person making Deposit: _____

Declaration Under 37 C.F.R. §§ 1.801-1.809

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Ton Logtenberg, hereby certify that I am the Chief Scientific Officer of Crucell Holland B.V., successor in interest of INTROGENE B. V. ("Introgene"), and declare that:

1. I am informed and believe that Introgene is the assignee of U.S. patent application serial no. 09/444,284.

2.

3. I am informed and believe that on December 12, 2001 Introgene made deposits of the following constructs:

4.a construct pBR/AD.BAMRFIB16.PAC under number ECACC 01121709;

5.a construct pBR/AD.BAMRDELTAFIB.PAC under number ECACC 01121708;

6.a construct pBR/AD.BAMRFIB16 under number ECACC 01121710;

7.a construct pWE/Ad.AflIIrITRFib16 under number ECACC 01121711; and

8.a construct pWE/Ad.AflIIrITRDE2AFib16 under number ECACC 01121712

9.under the provisions of the Budapest Treaty with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty.

10.

11. On behalf of Introgene, I state that all restrictions upon public access to the deposit (except those permitted by 37 C.F.R. § 1.808(b)) will be irrevocably removed upon the grant of a U.S. patent on this U.S. patent application, and the deposit will be replaced if viable samples cannot be dispensed by the depository.

12.

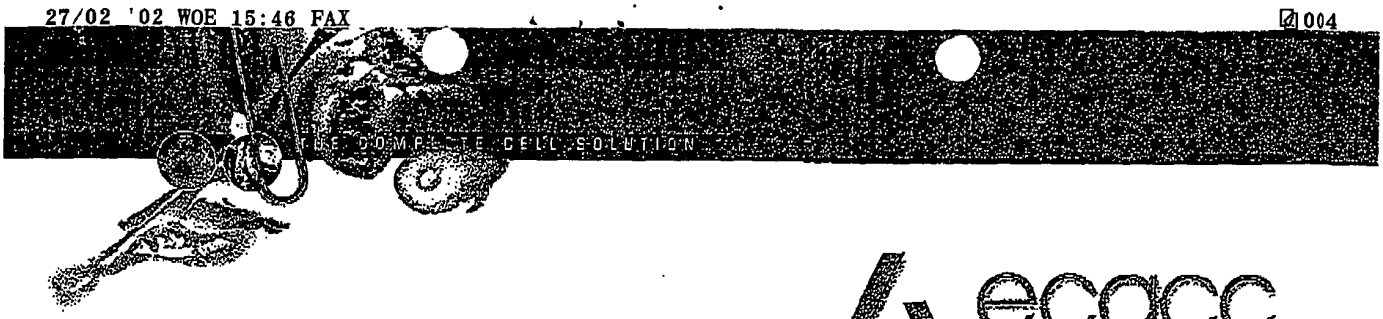
13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of the patent.

14.

15.

Date: 26-02-02.

Dr. Ton Logtenberg



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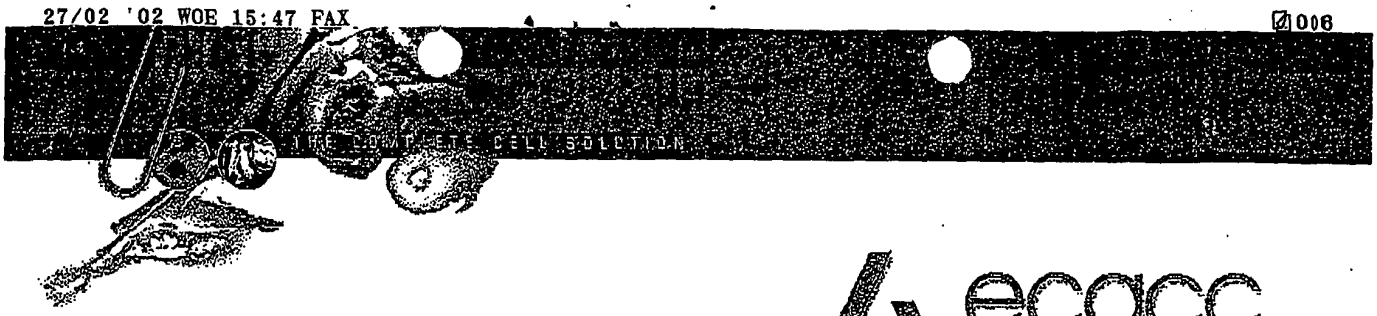

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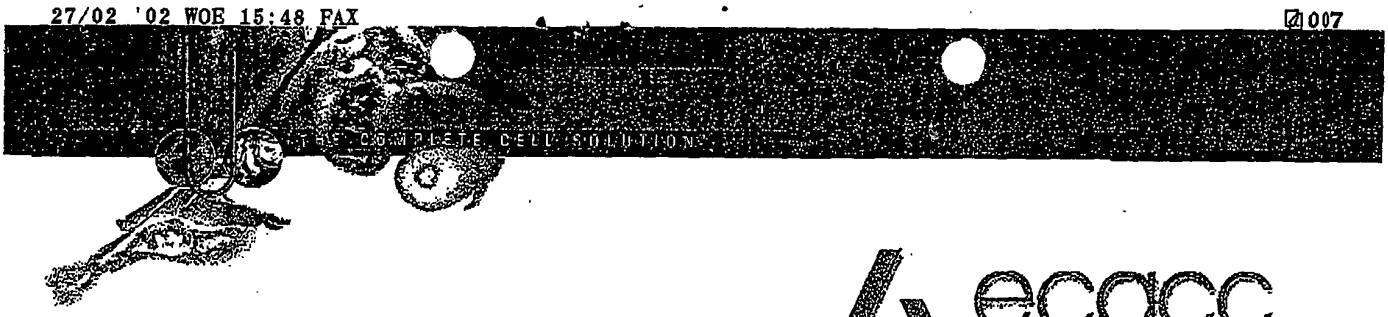

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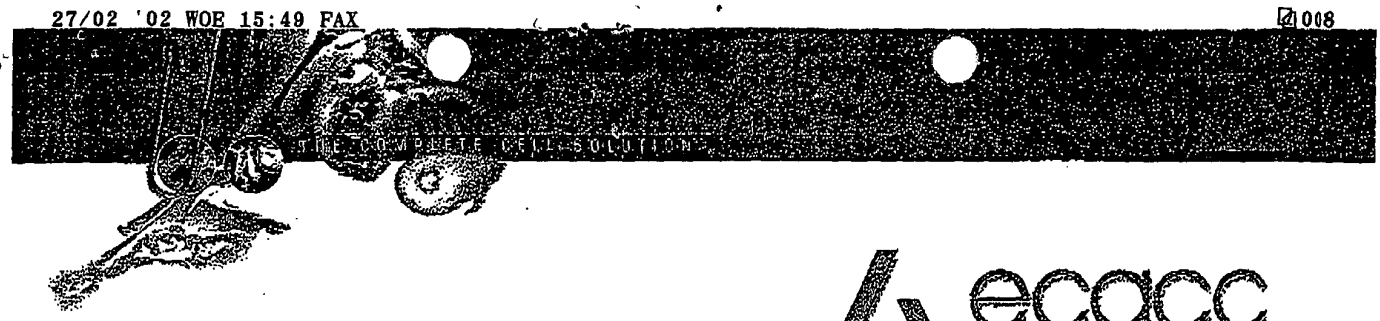

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